REMARKS

Claims 1-16 are pending in the application.

The Examiner has rejected claims 1-16 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,736,625 of Callstrom *et al.* ("Callstrom") taken in view of U.S. Patent No. 4,642,335 of Miyashiro *et al.* ("Miyashiro"). As basis for the rejection the Examiner reasons that Callstrom discloses compounds comprising a protein covalently bonded to a polymer through a linker group, and teaches that the linker group is a polyol having hydroxyl groups and the polymer is an acrylic polymer having a carbonyl group. Thus, the Examiner states that Callstrom provides "a substance (protein) bonded to a polymer surface comprising a carbonyl group via a linker having functional groups as claimed by the applicants. The Examiner concedes that Callstrom is deficient in that it does not provide a process to break the bond between the polymer and the linker. This deficiency is allegedly remedied by the teaching of Miyashiro that hydrogen bonds and a hydrophobic bonds are broken by extraction with methanol. Methanol, according to the Examiner, is an alkanol and thus meets the limitations of claims 1, 5, 7, 9, 11, 13 and 15. With regard to the remaining claims, one of skill in the art would have been capable of determining the optimal concentration of methanol by routine experimentation.

The applicants respectfully traverse the rejection.

Callstrom describes a method of stabilizing a protein in its native state to retain a functional property of the native protein in a hostile environment. The compounds of Callstrom comprise a protein covalently bonded to a polymer through a linker group. The protein of the compound is stabilized so that under hostile conditions an intended functional property of the protein is maintained to be at least equal to the native protein or it is enhanced over a reduced activity that the protein would not ordinarily exhibit in hostile conditions. The linker group is covalently bonded to the polymer main chain through an ester, amide, ether, thioether, thioester, peptide (one or more amide linkages), or a carbon to carbon linkage. Moreover, the linker group is covalently bonded to the protein through an ester, amide, ether, thioether, thioester, peptide (one or more amide linkages) or amine linkage. Since Callstrom stresses that it is desirable to

stabilize the protein so that it will retain its active and/or catalytic properties in a hostile environment, no teaching of separating the protein from the polymer is taught or suggested.

Miyashiro teaches anthracycline compounds bound to hydrophilic polypeptides. The anthracycline compound and the polypeptide are bonded by hydrogen bonding or by ionic bonding or a combination thereof. Because of the bonding, the new anthracycline compounds disclosed in Miyashiro exhibit higher carcinocidal activity and broader carcinocidal spectrum accompanied by less toxicity. Miyashiro provides the following disclosure:

> The compounds of this invention, in which a hydrophilic polypeptide and an anthracycline anti-tumor substance are combined through a hydrogen bond and/or a hydrophobic bond, behave as a single polymer in water. But these bonds are broken to liberate the two components if the compounds are treated under certain conditions, such as treatment with 8*M* solution of urea (cleavage of hydrogen bond), treatment with 1% solution of sodium dodecylsulfate (hereinafter abbreviated as "SDS"), and extraction with methanol or ethyl acetate (cleavage of hydrophobic bond).

Col. 4, ll. 22-33 (emphasis added).

In order to establish a *prima facie* case of obviousness based upon a combination of references, the Examiner must establish: (i) that the combination teaches or suggests all elements of the invention as claimed; (ii) that there is some motivation or suggestion in the art that would have caused a person of skill to make the combination as proposed by the Examiner; and (iii) that a person of skill in the art would have had a reasonable expectation that making such combination would be successful. In the present situation the Examiner has failed to make a *prima facie* case of obviousness.

First, the combination of references as taught by the Examiner neither teaches nor suggests all elements of the invention. Callstrom provides a protein bound to a polymer. However, as is clear from the disclosure of Callstrom, the protein is covalently bonded to the polymer through a linker group (*see* Col. 7, ll. 23-24). Moreover, the linker group is covalently bonded to the polymer main chain through an ester, amide, ether, thioether, thioester, peptide (one or more amide linkages), or a carbon to carbon linkage. *See* Col. 7, ll. 49-52. The hydroxyl groups present on the linker in Callstrom do not form hydrogen bonds attaching the protein to the polymer surface, but act to stabilize the protein that is covalently bonded to the polymer structure in an environment where it is liable to undergo denaturation. *See also* Examples 8 and 10 of

Callstrom (confirming that amide bonds exist between the linker and the polymer surface, not hydrogen bonds).

The disclosure of Miyashiro does not remedy this deficiency for no conjugate containing a polymer linked to a protein by a hydrogen bond is disclosed.

In addition, the combination of references proposed by the Examiner teach that the hydrogen bond between the linker and the surface is separated by adding a polar organic solvent. Contrary to the Examiner's assertion, Miyashiro unambiguously discloses that the hydrogen bond of the anthracycline-polypeptide compound is broken through use of an 8*M* solution of urea. Urea is not a polar organic solvent. In contrast, the claimed invention requires that the hydrogen bond existing between the linker and the polymer is separated by a polar organic solvent.

Moreover, a person of ordinary skill in the art would have had no motivation to make the combination proposed by the Examiner, nor would he have had any reasonable expectation that the combination would be successful. Callstrom is directed to stabilizing complex proteins such as enzymes and antibodies such that they retain their tertiary and quaternary structure in a hostile environment such that the catalytic activity of an enzyme and/or the capacity of an antibody to recognize a specific ligand is not lost in that environment. Thus, to make a combination that would cause a separation of the stabilized proteins from the agents which stabilize it would render the Callstrom invention useless, and be contrary to the aims furthered by the Callstrom invention. Accordingly, a person of ordinary skill in the art would not have been motivated to combine Callstrom with the bond separating technique taught in Miyashiro.

Therefore, in view of the foregoing, it is respectfully requested that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a) based upon the combination of Callstrom and Miyashiro.

CONCLUSION

It is submitted that claims 1-16 are fully compliant with the criteria of patentability. Accordingly, it is requested that the Examiner reconsider the rejection and allow the claims at the earliest opportunity.

Respectfully submitted,

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30 April 2004
(Date)

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